EFFECT OF ALBUMIN ADMINISTRATION PRIOR TO GRAFT REPERFUSION ON THE SEVERITY OF REPERFUSION SYNDROME DURING LIVING RELATED LIVER TRANSPLANTATION

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ABSTRACT

A prospective randomized study to evaluate the effect of intra-operative use of Albumin (20%) infusion prior to graft reperfusion on the severity of reperfusion syndrome during living donor liver transplantation. Twenty patients were included with Child-Pughs C classification (ESLD). Samples and measurements were taken prior to reperfusion, during and after reperfusion of the donor liver graft. I.V. fluids, blood and blood products were used to adjust a Hb level at (8-10 gm/dl) and Hct between 24-28% for better graft function and survival. The reperfusion syndrome was severe as regard the decrease in MABP in No Albumin group (MABP = 48.2±7.23 mmHg) compared to Albumin group (MABP = 63.45±6.96 mmHg), (P=0.0002) CVP was highly significant increased in Albumin group during reperfusion compared to No Albumin group (p = 0.0002). Also, CVP correlated positively with S. albumin level (r = 0.81, p = 0.002) during reperfusion syndrome. Patients of No Albumin group needed more inotropic support than patients of Albumin group. In conclusion Albumin 20% in a dose of 1.5 ml/kg causes volume retention and expansion of intravascular volume which was a beneficial effect in liver transplant surgery to elevate the CVP prior to graft reperfusion and hence decreasing the severity of reperfusion syndrome and also elevating the already low serum albumin level and oncotic pressure.

INTRODUCTION

Graft reperfusion in liver transplants is associated with reperfusion syndrome, which includes hemodynamic instability, hypotension and decreased systemic vascular resistance. This usually requires administration of fluids, vasopressors and inotropes.[1-3] It was found that the severity of the reperfusion syndrome correlates with lower central venous pressure (CVP) during the dissection phase.[4]

Serum albumin is the main determinant of plasma colloid osmotic pressure (oncotic pressure), and it helps to keep fluids in the intravascular compartement. Low serum albumin concentration is seen in a variety of diseases including end stage liver disease (ESLD).[5,6]

Many studies[7] found that albumin administration decreased fluid requirements, increased colloid oncotic pressure and decreased the incidence of pulmonary edema in cardiac and non cardiac surgery. In hypoalbuminaemia and ESLD, higher doses of albumin reduced morbidity. In ascites associated with liver recipients, albumin reduced hemodynamic derangements and improved survival after spontaneous bacterial peritonitis.[6] In sepsis, albumin decreased pulmonary edema and respiratory dysfunction compared with crystalloids.[6-9]

Alternatives for albumin for expansion of the intravascular volume and elevation of the CVP are available. However, they are not without side effects. Hetastarch impairs platelets aggregation, prolongs bleeding time and decreases the level of circulating factor VIII.[10] It also remains in the reticulo-endothelial system for long time. Gelatin based plasma expanders can cause anaphylactic reactions, decrease thrombin generation and impair primary hemostasis through reduction in von Willebrand factor activity, all these effects aggravated by fibrinolysis already present during transplant surgery.[11,12]

The aim of this study is to evaluate the effect of albumin administration prior to graft reperfusion on the severity of reperfusion syndrome and the requirements of vasopressors and inotropes in post-reperfusion period.

PATIENTS AND METHODS

Twenty adult patients (ASA-II-III), with Child-Pughs C classification, undergoing living-related donor liver transplantation were evaluated in this study. Following Ethics committee approval and informed consent.

Patients were divided into two groups (10 patients each).

1- Albumin group: For these patients in addition to regular I.V, maintenance fluids; Human albumin 20% was given in a dose of 1.5 ml/kg immediately prior to graft reperfusion.
2- No albumin group: For these patients regular I.V fluids were only given.

All patients of both groups received blood and blood products (Packed RBCs and plasma) to keep Hb level at 8-10 gm/dl and Hct at 24% - 28%.

General anaesthesia was induced with propofol 2 mg/kg, atracurium 0.6 mg/kg and fentanyl 2 µg/kg. Isoflurane and mixed air/oxygen were used for maintenance. Intraoperative incremental doses of muscle relaxants guided by peripheral nerve stimulation as well as repeated doses of fentanyl was used to maintain a state of balanced anaesthesia and analgesia during surgery. The right internal jugular vein was cannulated with a triple lumen central venous catheter using Seldinger technique. A left radial artery cannuale was inserted for monitoring the systemic blood pressure invasively. All patients were kept warm with external forced warm water mattress and warm intravenous devices. MABP, CVP and serum albumin level were measured just prior to reperfusion, during and every 1h for 3 hourspost graft reperfusion, also ephedrine doses and inotropic supports.

Statistics: Data presented as median (interquartiles) for statistical analysis by Wilcoxan-Signed Ranked test, using the SPSS computer softwate (SPSS 10 for Window; SPSS Inc., Chicago, IL). A p value of < 0.05 was considered to be statistically significant.

RESULTS

Twenty patients were involved, 10 patients in each group. Patients characteristics and demographic data were comparable between both groups (table 1). Viral hepatitis C constituted the main cause for the ESLD.

MABP decreased during reperfusion of donor graft with the recipient portal blood (reperfusion syndrome), the reperfusion syndrome was severe ($p = 0.0002$) in No Albumin group (MABP = 48.20 ± 7.23 mmHg) compared to Albumin group (MABP = 63.45 ± 6.96). During the postreperfusion period (1st, 2nd & 3rd hr). MABP showed significant decrease in No Albumin group compared to Albumin group (Table 2).

Preoperative hypo-albuminaemia was always present among patients of both groups. Mean albumin level was 2.18 ± 2.09 gm/dl in Albumin group and 2.20 ± 2.03 gm/dl in No Albumin group. During reperfusion s. albumin level increased insignificantly in albumin group (3.14 ± 2.78). Compared with No Albumin group by about 0.82 g/dl.

The mean CVP showed no significant differences between both groups, prior to reperfusion (11.03 ± 0.8 in AI group) and (10.06 ± 1.2 in NOA/b group). During reperfusion it was highly significantly increased to Albumin group (13.1 ± 1.12 cm H_2O) compared at No Albumin group (7.3 ± 1.02 cm H_2O) and continued to be higher during post-reperfusion period ($p = 0.001$), (Table 4).

CVP correlated positively with S. albumin level ($r = 0.81$, $p = 0.002$) during reperfusion syndrome (Table 6).

Patients of No Albumin group needed more vasopressor support in the form of high ephedrine doses during reperfusion syndrome (10.63 ± 1.97 mg) with significant increase in doses compared to Albumin group (5.38 ± 2.13 mg), also ephedrine was continued to be used during 1st and 2nd hour post-reperfusion in No Albumin group. (Table 5).

Table (1): Demographic data

	Alb. Group	No Alb. group	P
Age (years)	42.8±7.13	41.6±8.27	0.28
Weight (Kg)	71±14	74±16	0.105
Sex (M/F)	7/3	8/2	0.39
Duration of anaesthesia (hr.)	13±1.8	14±1.3	0.25

Alb = Albumin

Table (2): Mean Arterial Blood pressure (mmHg) in both groups. (mean ±SD)

		Prior to reperfusion	Rep.	Post reperfusion		
				1h	2h	3h
Alb. Group	Mean	82.40	63.45	78.61	80.96	85.40
	SD	4.26	6.96	5.52	7.08	5.68
No Alb.	Mean	81.90	48.20	53.30	69.1	73.70
Group	SD	5.68	7.23	8.43	4.72	6.50
P		0.28	0.0002*	0.0001*	0.0001*	0.004*

* Significant (p < 0.05).
Rep = reperfusion

Table (3): S. Albumin (g/dl) level in both groups. (mean ±SD)

		Prior to reperfusion	Rep.	Post reperfusion
Alb. group	Mean	2.18	3.14	3.67
	SD	2.09	2.78	3.02
No Alb. group	Mean	2.20	2.32	2.20
	SD	2.03	1.96	1.82
P		0.56	0.28	0.09

* Significant (p < 0.05).

Table (4): Changes in CVP in both groups. (Cm H_2O) (mean ±SD)

		Prior to reperfusion	Rep.	Post reperfusion
Alb. group	Mean	11.03	13.10	12.9
	SD	0.89	1.12	1.03
No Alb.	Mean	10.60	7.30	7.20
Group	SD	1.26	1.02	1.06
P		0.107	0.00025*	0.001*

* Significant (p < 0.05).

Table (5): Ephedrine doses in both groups (mg). (mean ±SD)

		Prior to reperfusion	Rep.	Post reperfusion		
				1h	2h	3h
Alb. group	Mean	0	5.38	0	0	0
	SD	0	2.13	0	0	0
No Alb.	Mean	0	10.63	7.30	2.10	0
group	SD	0	1.97	2.02	1.82	0
p		-	0.0001*	-	-	-

* Significant (p < 0.05).

Table (6): Correlation between serum albumin and CVP. (mean ±SD)

S. albumin # CVP	R	p
Prior to rep.	0.46	0.19
Reperfusion.	0.81	0.002*
Post Rep.	0.42	0.103

* = Significant (P<0.05)

DISCUSSION

The debate over giving colloids or crystalloids for fluid replacement and volume expansion has been started since the 19th century[13] and still going on. Until this debate is settled, physicians will continue to use a mix of both crystalloids and colloids guided by their own experience.[14] In the present study, we evaluated the effect of temporarily increasing the CVP prior to graft reperfusion on the severity of reperfusion syndrome and

the requirements of vasopressors and inotropes in the post-reperfusion period. It was found that reperfusion syndrome was, severe (MABP = 48.2 ± 7.23 mmHg, CVP = 7.3±1.02 cm H_2O) in No Albumin group patients and the decrease in MABP and CVP was long lasting in post-reperfusion period, while the effect of reperfusion syndrome was limited and of short duration in Albumin group patients. (MABP = 63.45±6.96, CVP = 13.1±1.12)

In view of the low albumin level in liver transplant recipients, using albumin 20% bolus dose just prior to reperfusion was considered, aiming to get benefit of the sudden circulatory distension[15] with elevation of the CVP as well as elevating the serum albumin level. However, there are several reports which question the safety and efficacy of albumin administeration. The Cochrane review of 30 randomised controlled trials concluded that there is no evidence that albumin administration reduces mortality in critically ill patients with hypovolemia, burns, or hypo-albuminemia, they suggested that it may increase mortality by 6%.[5] Although low albumin level is a marker of critical illness and is associated with increased mortality,[5,15] a direct causal relationship has not been established. Furthermore, hypoalbuminemia is usually a result rather than a cause of serious illness. Soni[16] wrote that there is no convincing evidence for using albumin either to replace volume or to treat low concentrations of serum albumin guidance from the UK transfusion service states[17] "20% albumin can produce severe circulatory overload and 5% albumin should be used with caution in patients at risk of sodium retention". And the Cochrane review[5] invited for further research in the issue of albumin administration. A recent systemic review[7] of seventy nine randomized controlled trials found albumin to have benefits in a variety of clinical situations such as cardiac and hepatic surgeries in view of decreasing the incidence of pulmonary edema.

Argument in favor of albumin in case of massive loss of blood during extensive hepatic and transplant surgery is strong. Replacement with red cells and crystalloid or artificial colloids dilutes serum components, albumin among them. Initially the losses will be restored from the tissue pool. When a certain threshold is exceeded, however the tissue pool gets depleted. Once this situation has occurred infusion of albumin no longer prevents the slide into multiple organ failure and death.[18]

In addition to expansion of intravascular volume and support of colloid oncotic pressure, albumin is a carrier protein that has a transport function. It also binds some substances that are active, or toxic only in the free form. In addition albumin is a free radical scavenger and plays a role in maintaining microvascular integrity,[19] So living related donor graft will benefit from this effect.

In liver transplant surgery we also aim for a hematocrit value of 24 to 28% for proper graft function, so we tolerate some blood loss without administration of packed red cells. Administration of fresh frozen plasma is only indicated to correct coagulation abnormalities as guided by coagulation profile. As regards crystalloids, up to five times more volume than albumin 4.5% is needed to produce the same sustained elevation of intravascular volume,[20] with problems of fluid overload, hyperchloremia, and pulmonary edema.

In conclusion, Albumin 20% causes volume retention of up to four folds,[21] causing expansion of the intravascular volume. This is consider as a beneficial effect in liver transplant surgery to elevate the CVP prior to graft reperfusion and hence decreasing the severity of reperfusion syndrome and in the mean time elevating the already low s. albumin level and oncotic pressure. The volume of albumin 20% used (1.5 ml/kg) is no more than what is given during tapping of ascites.

REFERENCES

1. Koelzow H, Gedney JA, Baumann J et al. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. Anesth. Analg. 2002; 94(4): 8249.
2. Ricciardi R, Foley DP, Quarfordt SH et al. Donor hepatic function; a factor in post-reperfusion syndrome. J. Gastrointest Surg. 2002; 6(2): 248-54.

3. Malenaar IQ, Begliomini B, Martinelli G et al. Reduced need for vasopressors in patients receiving aprotinin during orthrotopic liver transplantation. Anesthesiology. 2001; 94(3): 433-8.
4. Ayanoglu HO, Ulukaya S, Tokat Y. Causes of post-reperfusion syndrome in living or cadaveric donor liver transplantations. Transplant Proc. 2003; 35(4): 1442-4. (Abstract).
5. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: Systematic review of randomized controlled trails. BMJ 1998; 317: 235-240.
6. Goldwasser P, Feldman J, Association of serum albumin and mortality risk. J Clin Epidemiol 1997; 50: 693-703. (Abstract).
7. Haynes G, Navickis R, Wilkes M. Albumin administration-what is the evidence of clinical benefit ? A systematic review of randomized controlled trails. Eur J Anaesthesiol. 2003; 20: 771-93.
8. Nel MR, Human albumin administration in critically ill patients, critical analysis of original studies has to take place. Letter. BMJ 1998; 317: 882.
9. Beale R, Wyncoll D, McLuckie A. Human albumin administration in critically ill patients. Analysis is superficial and conclusions exaggerated. BMJ 1998; 317-382.
10. Falk JL, Rackow EC, Astiz ME, Weil MH. Effects of hetastarch and albumin on coagulation in patients with septic shock. J Clin Pharmacol. 1988; 28: 412-415.
11. De Jonge E, Levi M, et al. Impaired haemostasis intravenous administration of a gelatin-based plasma expander in human subjects. Thrombosis and Haemostasis 1998; 79: 286-290. (Abstract).
12. Hartmut J. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Gastrointest. Liver physiol. 2003; 248: G 15-26.
13. Hankeln KB, Beez M. Haemodynamic and oxygen transport correlates of various volume substitutes in critically ill in-patients with various aetiologies of haemodynamic instability. Int J Intensive Care 1998; 5: 8-14. (Abstract).
14. Watts J, Fluid resuscitation with colloids or crystalloid solutions. Comparing different studies is difficult. Letter, BMJ. 1998; 317: 277.
15. McClelland B. Albumin: Don't confuse us with the facts rather than fulminating, seek to answer questions raised. BMJ 1998; 317: 829.
16. Soni N. Wonderful albumin ? Not all it is cracked up to be. BMJ. 1995; 310: 887-888.
17. McClelland DBL. Hand book of transfusion medicine. 2nd ed. London: HMSO, 1996.
18. Kaag M, Zoetmulder F. Human albumin administration in critically ill patients. More research into proper use of albumin is needed. Letter BMJ 1998; 317: 882.
19. Horsey P. Albumin again. Letter BMJ 1999; 318: 1352.
20. Demling R. Effect of plasma and interstitial protein content on tissue edema formation. Curr Stud Hematol Blood Transfus 1986; 53: 36.
21. Offringa M. Excess mortality after human albumin administration in critically ill patients. Clinical and pathophysiological evidence suggests albumin is harmful. BMJ 1998; 317: 223-224.